



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2021-D-1311]

Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a final guidance for industry entitled “Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic.” The COVID-19 pandemic has resulted in a significant reduction in the supply of nonhuman primates (NHPs) available for conducting toxicology studies for new pharmaceuticals. This has the potential to significantly delay the development of new medications for the treatment of diseases currently without effective treatment options. This guidance provides FDA’s recommendations to industry to help mitigate the NHP supply issue by reducing the demand for NHPs during the COVID-19 pandemic. Given the public health emergency presented by COVID-19, this guidance document is being implemented without prior public comment because FDA has determined that prior public participation is not feasible or appropriate, but it remains subject to comment in accordance with the Agency’s good guidance practices.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2021-D-1311 for "Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at

<https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:
<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001

New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or the Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Ronald Wange, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 3342, Silver Spring, MD 20993-0002, 301-796-1304; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a final guidance for industry entitled “Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic.”

The COVID-19 pandemic has caused a marked reduction in the supply of NHPs available for conducting nonclinical toxicity assessments. Before the pandemic, China was the largest supplier of NHPs used in pharmaceutical development, accounting for 60 percent of NHPs imported to the United States.¹ Early in the pandemic, China implemented a ban on the trade of wild animals--including NHPs--in an effort to potentially curb the spread of SARS-CoV-2. This ban remains in effect. In conjunction with this reduction in supply, there has been a substantial

¹ See “Rapid Response by Laboratory Animal Research Institutions During the COVID-19 Pandemic: Lessons Learned: Proceedings of a Workshop--in Brief”; available at <https://www.nap.edu/catalog/26189/rapid-response-by-laboratory-animal-research-institutions-during-the-covid-19-pandemic-lessons-learned>.

increase in the demand for NHPs for the testing of experimental COVID-19 treatments and vaccines.²

This reduction in supply and prioritization for COVID-19-related studies have severely restricted the availability of NHPs for other pharmaceutical development programs, resulting in a disruption in supply that has the potential to significantly delay the development of new medications for the treatment of diseases currently without effective treatment options. While the disruption affects the NHP supply generally, there is a particularly acute shortage of sexually mature NHPs that are often the only pharmacologically relevant species with which to assess developmental and reproductive toxicity endpoints for biotherapeutic proteins (biological products).

This guidance provides recommendations regarding the use of NHPs in development programs for small molecule drugs as well as for biological products, covering both general toxicity studies and developmental and reproductive toxicity (DART) studies. The guidance provides FDA's recommendations for sponsors to use alternative nonrodent species, whenever possible, in general toxicology studies and, in general, to not use NHPs for DART assessment of small molecule drugs. For DART studies of biological products, the guidance provides FDA's recommendation that sponsors fully utilize non-NHP approaches to assess DART. These approaches include, when scientifically appropriate, the use of a weight-of-evidence approach to risk assessment, the use of species-specific surrogate proteins in rodents, and the use of rodents genetically modified to (1) respond to the clinical candidate or (2) evaluate the effects of altered activity of the target of the biological product. In instances with no scientifically appropriate alternatives to the NHP, the sponsor may be able to reduce the number of NHPs used per study by reducing the number of treatment groups in the study. The guidance also addresses the potential for delaying the conduct of DART studies to the postmarketing setting. Taken together,

² FDA supports the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method is adequate to meet the regulatory need.

these recommendations are expected to help mitigate the constrained supply of NHPs until such time as the NHP supply recovers sufficiently from the effect of the COVID-19 pandemic.

In light of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS), pursuant to section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)), FDA has determined that prior public participation for this guidance is not feasible or appropriate and is issuing this guidance without prior public comment (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(h)(1)(C)(i) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practice statute and regulation.

This guidance is intended to remain in effect for the duration of the public health emergency related to COVID-19 declared by the Secretary of HHS, including any renewals.³ However, the recommendations and processes described in the guidance are expected to help mitigate the COVID-19 pandemic-related NHP supply constraints affecting pharmaceutical development that are expected to persist beyond the termination of the COVID-19 public health emergency (e.g., time required to rebuild breeding stocks and for NHPs to reach sexual maturity) and reflect the Agency's current thinking on this issue. Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic." It does not establish any rights for any person and is not binding on FDA or the

³ See <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001; the collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014; and the collections of information in 21 CFR part 601 have been approved under OMB control number 0910-0338.

III. Electronic Access

Persons with access to the internet may obtain the guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, or <https://www.regulations.gov>.

Dated: February 16, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.